



Stenotrophomonas Maltophilia Nosocomial Infections and Clinical Challenges

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Summary

Objective: To analyze the use of antibiotic therapy in nosocomial infections.

Method: It consists of a qualitative, descriptive and exploratory study. To gather their literature, a narrative review was carried out, a traditional method of review in which the selection of articles does not follow a systematic model and the author can include documents according to his bias, without explicit definition criteria. The research was carried out on the PubMed platform, using the descriptors "*Stenotrophomonas maltophilia*", "infection", "resistance" and "treatment". Complementary research was also carried out in the Virtual Health Library (VHL). The work was structured in 15 articles, which responded to the proposed criteria, in English, Portuguese and Spanish.

Results: The studies show that there are challenges in medical care regarding the treatment of nosocomial infections and, therefore, it is necessary to develop ways to improve the implemented actions and interventions. The publications show the importance of correct antibiotic therapy and point out that professionals must strive to meet the needs of users and the community, providing a quality service that generates satisfaction.

Conclusion: Antibiotic therapy should be discussed and considered in the treatment of nosocomial infections, from the prevention of organic damage to the reduction of problems after the installation of the problem. Despite the need for further studies to define which prescription will be more effective, it can be concluded that the use of a broad spectrum can already be considered in clinical practice after individual assessment of patients.

Keywords: *Stenotrophomonas maltophilia*; infection; resistance; treatment

Introduction

Stenotrophomonas maltophilia is a non-fermentative gram-negative environmental bacillus first identified in 1943 as *Bacterium bookeri*. Since then, it has occupied a diversity of ecological niches, such as soils, plants and multiple water sources

[1]. In the hospital environment, there is evidence of bacterial isolation from tap water, dialysis equipment, mechanical ventilators, catheters, endotracheal tubes, and occasionally from the hands of healthcare professionals [2]. The microorganism in question is the only species of the genus *Stenotrophomonas* capable of infecting

humans and has emerged in recent years as a nosocomial pathogen, mainly associated with lower respiratory tract infections and blood infections, such as pneumonia and bacteremia, respectively [3]. As the virulence is relatively low, its presence in the oropharyngeal microbiota of healthy patients is rare, with greater recurrence in immunocompromised and hospitalized patients, mainly in those in the Intensive Care Unit (ICU) undergoing prostheses, being associated with high rates of morbidity and mortality [4]. Thus, the clinical challenges related to infection by *S. maltophilia* are associated with molecular heterogeneity and the intrinsic resistance of its strains to several antibiotics, including aminoglycosides and carbapenems, in addition to the relevant formation of biofilms. Despite the undeniable clinical impact, there are still gaps regarding the microbiological characteristics, risk factors and mechanisms used by these opportunistic pathogens during infection and disease, which impact on the treatment of infections and consequently lead to outbreaks in Brazil and worldwide.

Materials and Methods

Characterization of the research

The present study is characterized by its qualitative, descriptive and exploratory nature. To gather scientific data from the literature, a narrative review was performed, a traditional review method in which the selection of articles does not follow a systematic model and the author can include documents according to his bias, without explicit definition criteria [5]. In view of this, the PICO strategy was used to elaborate the following research guiding question: "How has *Stenotrophomonas maltophilia* become a challenge in the context of nosocomial infections?"

Conducting the investigation and selection criteria

The scientific search was carried out during the month of February 2023, from the PubMed and Virtual Health Library (VHL) databases. The descriptors used were "*Stenotrophomonas maltophilia*", "infection", "resistance" and "treatment", which are associated in different ways with the Boolean operator "AND". In addition, the criteria used for sample selection were publications that explicitly point out, in their abstract and title, references on the mechanisms associated with nosocomial infections by the target pathogen. These publications should correspond to complete texts, published in Portuguese, English and Spanish, without temporal cuts and with free access. The data collection of the study occurred before the individual analysis of each bibliography, correlating the findings to the theme proposed in the research.

Presentation of findings and Synthesis of information

After reading the works in full, the research was designed as a descriptive and exploratory dissertation, organized from the synthesis and critical analysis of 15 articles, with the objective of answering the guiding question of the investigation and providing the state of the art on the subject moreover, we also sought to extract findings considered innovative for the clinical approach to infections caused by *S. maltophilia*. It is noteworthy that there

was no need to submit the study to the Research Ethics Committee (CEP), in view of the use of public data and the fact that the research was not carried out on human beings.

Risk Factors and Susceptibility to Infection

Gram-negative bacterial pathogens require careful attention, as they are often associated with multidrug-resistant infections, especially in immunocompromised individuals. Its transmission to susceptible individuals does not depend on age and can occur through direct contact with the source. In ICUs, for example, the hands of health professionals have already been reported as potential transmitters of infection [6]. According to the literature, among the underlying diseases, Chronic Obstructive Pulmonary Disease (COPD) leads to the risk of infection, followed by malignant tumors. However, underlying diseases such as Diabetes Mellitus, renal failure and immunodeficiency disorders do not have a significant relationship with the development of *S. maltophilia* pneumonia in the ICU, as well as the use of corticosteroids. With regard to invasive maneuvers, the main association is with mechanical ventilation, accompanied by tracheostomy and tracheal intubation, given that such procedures make it possible to break down basic body barriers and predispose to the formation of biofilms. The duration of the interventions is also linked to the susceptibility of the infection, so that the risk increases with the time the devices are used [7].

Although mainly described as a respiratory pathogen, *Stenotrophomonas maltophilia* also appears as an etiological agent of urinary tract infections, with significant morbidity. Associated risk factors include underlying urological or nephrological diseases, immunocompromise, use of indwelling catheters and other invasive devices, extended antibiotic treatment, as well as prolonged ICU stay. Similar to the mechanisms developed by invasive maneuvers in respiratory infections, vulnerability to these microorganisms is partially explained by the formation of biofilms in catheters, B-lactamases and SmeDEF pumps, which guarantee multiple modes of resistance to antibiotics [8]. Therefore, it is observed that the multifactorial nature of this infection is based on the development of protection mechanisms against the host's natural defenses, which explains its high incidence in immunocompromised patients. Therefore, it is essential to understand the risk factors associated with the disease, since the versatility and complexity of the pathogen protects it from several control measures and challenges the care of critically ill patients.

Mechanisms Associated with Antimicrobial Resistance

The bacterium *S. maltophilia* exhibits a high profile of antimicrobial resistance due to inherent and acquired antibiotic resistant genes. Furthermore, all strains of this species have been shown to harbor resistance genes [9-11]. This implies that strains resistant to quinolones, cotrimoxazole (TMP-SMX), cephalosporins and other conventional therapies for *S. maltophilia* infections are becoming recurrent. In a Canadian hospital setting, for example,

erythromycin and tetracycline resistance genes were detected in 100% of collected air samples (containing the microorganism) from hospital rooms [12,13]. In Korea, they observed that the *sul1* antibiotic resistance gene (ARGs) within class 1 integrons rather than *sul2* were responsible for resistance to TMP-SMX. In the bacterium under study, they may be linked to multiple ARGs within Class 1 integrons [14]. In addition to this altered characteristic, it was verified in other ARGs that the macrolide phosphotransferase (*mphBM*) among a set of genes (such as the heavy metal tolerance gene), cadmium efflux determinant (*cadA*), as well as its transcriptional regulator gene (*cadC*) has been reported in *S. maltophilia* D457. Furthermore, the determinants of chromosomal resistance to aminoglycosides, also known as aminoglycoside-modifying enzymes (AMEs), arise from AME genes, which in turn are the predominant genetic resident in class 1 integrons of *S. maltophilia*. All the attributes of these bacteria lend further credence to the need to incorporate isolates such as *S. maltophilia* and *Acinetobacter* species as test isolates in drug screening [15].

Impasses in the Therapeutic Approach

The limited therapeutic arsenal of *Stenotrophomonas maltophilia* has been a matter of concern among clinical microbiologists and the medical community. It occurs due to the presence of two B-lactamase enzymes (L1 and L2), which eliminate virtually all B-lactams as treatment options. In this sense, the main therapeutic agents for this infection turn to the use of non-B-lactam drugs with intracellular targets, although their activity also suffers limitations due to the range of efflux pumps present in this pathogen [1]. Since the 1990s, when an in vitro antimicrobial susceptibility study was developed, trimethoprim-sulfamethoxazole has been the non-B-lactam drug of choice for the treatment of *S. maltophilia* infections, acting as an antimetabolite. However, due to its frequent adverse effects, such as hypersensitivity reactions, and the increasing rate of resistance, there was a need to acquire potent alternative antibiotics. In this context, fluoroquinolones have emerged as a popular option for the treatment of these infections, which, so far, have not shown inferiority to trimethoprim-sulfamethoxazole in comparative studies. However, there are still shortages of randomized clinical trials or meta-analyses on this issue [16]. Of the second-line antimicrobials, Minocycline is the most reliable antibiotic in in vitro tests, being susceptible in more than 99% of isolates, when considering its minimum expected inhibitory concentration (MIC \leq 4 μ g/ml).

Levofloxacin, on the other hand, under conditions of MIC in line with current pharmacokinetic-pharmacodynamic expectations for the drug (MIC \leq 0.5), presents susceptibility in less than 50% of isolated cases. Furthermore, cefiderocol, tetracycline derivatives and new B-lactamase inhibitors, such as aztreonam-avibactam, appear as drugs capable of bringing new perspectives for the treatment of *S. maltophilia*, however, the clinical utility of these therapies still remains limited [17]. Before the extreme difficulty of treatment, combined therapy has emerged as an option. However,

the threshold between the synergistic effects against bacteria and the adverse events of drug addiction may constitute an objection to this practice. According to studies, monotherapy was significantly better than combined therapy in the mortality outcome in patients with nosocomial pneumonia and susceptible to antimicrobials, however, in patients only infected with *S. maltophilia*, the mortality rate did not show significant variation [18]. Analysis of such findings suggests that combination therapy should be reserved for severe infections or infections that do not improve after monotherapy, which indicates the presence of multidrug-resistant strains. Based on the limited antimicrobial therapy available for *S. maltophilia* infections, the pathogen has been the object of study in numerous reviews, in an attempt to remedy the lack of clinical results capable of guiding therapy. However, the absence of reliable controlled trials contributes to the perpetuation of this problem and determines the status of emerging resistance [1].

Conclusion

Given the information brought in this study, we can conclude that *S. maltophilia* has a very dynamic character. This organism is not only an opportunistic pathogen in severe and life-threatening infections in vulnerable individuals but has also been reported as a unique pathogen in immunocompetent individuals. Additionally, we reiterate that the agent accompanies disease and death in patients with respiratory tract infection (RTI), especially in clinical conditions such as cystic fibrosis, bacteremia and/or urinary tract infection. Thus, the proper diagnosis must be made with caution, as the indiscriminate use of antibiotics can lead to increased myelosuppression and/or selection of resistant strains of the species. Thus, strict adherence to hygiene rules, quality control in hospital units and pharmaceutical companies, avoiding the abuse of antibiotics are important and defended measures, as these conditions predispose the body to antibiotic resistance. In addition, it is worth noting that these antimicrobial resistance genes in the organism can be transferred to other species and cause serious public health problems. Therefore, the use of such genes as markers for genetically modified crops should be discouraged.

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